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ORIGINAL ARTICLE

Bortezomib–dexamethasone versus high-dose melphalan for Japanese patients with systemic light-chain (AL) amyloidosis: a retrospective single-center study

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Abstract Bortezomib–dexamethasone (BD) and high-dose melphalan (HDM) are effective for systemic light-chain (AL) amyloidosis, but have not been compared in detail. We retrospectively investigated patients treated with BD or HDM at our center between September 2001 and June 2016. Among 234 patients, 20 were treated with BD and 30 received HDM. With the exception of age, transplant eligibility, and previous history of other chemotherapy, there were no significant differences in most background parameters between the two groups. Median age was higher (63.2 vs. 55.8, $P = 0.001$), number of transplant-eligible patients was lower (60.0 vs. 96.7%, $P = 0.002$), and number of previously treated patients was higher (35.0 vs. 0.0%, $P < 0.001$) in the BD group. The BD group showed trends toward lower treatment-related mortality (5.0 vs. 10.0%, $P = 0.641$), greater hematological response (partial response or better) (90.0 vs. 73.3%, $P = 0.279$), higher complete response (60 vs. 50%, $P = 0.487$), and similar survival with the HDM group (neither reached, $P = 0.705$). In conclusion, BD was as effective and safe as HDM. Notably, BD achieved this outcome among patients with poorer clinical backgrounds compared with HDM.

Keywords AL amyloidosis · Bortezomib · Dexamethasone · High-dose melphalan

Introduction

Systemic light-chain (AL) amyloidosis is an intractable disease in which abnormal plasma cell clone produces impaired monoclonal light chains in an unregulated manner, resulting in diffuse amyloid deposition and serious functional damage in multiple organs [1, 2]. The prognosis of patients with this disease was poor, with a median survival period of 13.2 months without effective therapeutic intervention [3]. In 1998, however, high-dose melphalan with stem-cell transplantation (HDM) was first reported and changed the treatment strategy and outcome of AL amyloidosis [4]. This has been considered as one of the first-line standard treatment options to the present [5]. On the other hand, a new class of chemotherapeutic agents with a novel mechanism of action, the proteasome inhibitors, was first reported in 2007, and showed favorable treatment efficacy when administered in combination with dexamethasone (bortezomib–dexamethasone; BD) [6], and bortezomib-based regimes have since come to play major roles in treatment [5]. The development of this new strategy raised the important clinical question of which option, bortezomib-based regimens or HDM, is safer and more effective. It is not possible to simply compare previously reported treatment outcomes, because each institution has different patient backgrounds and uses different treatment methodologies. However, there have been no prospective randomized studies or even retrospective cohort studies from a single center to address this question. Here, we report a retrospective single-center study analyzing the safety and efficacy of BD and HDM to provide insight into this clinical question.

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Table 1 Eligibility criteria of two regimens at our center

Bortezomib–dexamethasone	High-dose melphalan with stem-cell transplantation [7]
1. NT-proBNP <8500 pg/mL	1. No apparent signs or symptoms suggestive of congestive heart failure
2. ECOG performance status <grade 4	2. ECOG performance status <grade 3
3. Age <80 years	3. Age <65 years (until Apr. 2011), <70 years (after Apr. 2011)
	4. Systolic blood pressure >90 mmHg
	5. SaO_2 in room air >95%
	6. Fractional shortening of left ventricle > 35% on echocardiogram
	7. Serum creatinine <2 mg/dL
	8. Serum direct bilirubin <2 mg/dL
	9. Serum alkaline phosphatase <3 × the normal upper limit
	10. No associated chronic disorders such as cerebrovascular and pulmonary disease or severe diabetes mellitus

NT-proBNP N-terminal of the prohormone brain natriuretic peptide, *ECOG* Eastern Cooperative Oncology Group

Patients and methods

Patients

A total of 234 patients with systemic AL amyloidosis as confirmed either histopathologically or by mass spectrometry were identified in our database between September 2001 and June 2016 at the Shinshu University School of Medicine, Matsumoto, Japan. Those treated with BD or HDM were retrospectively included in this study, and patients that were treated with combined therapy using both BD and HDM were excluded. The eligibility criteria for each treatment option at our center are shown in Table 1. The criteria for HDM were derived from our previous study [7], and the BD criteria were newly determined by our center. After 2013, the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) cut-off point was added to the BD eligibility criteria, because NT-proBNP >8500 pg/mL was reported to be a significant predictor of very poor prognosis [8]. Patients fulfilling both BD and HDM eligibility criteria were treated accordingly with BD or HDM based on the results of discussion considering each patient's general condition and preference. The international consensus guidelines from the 10th International Symposium on Amyloidosis [9] and Mayo Clinic staging system 2012 [10] were used to determine organ involvement and clinical stage, respectively.

Treatment

In the BD regimen, 0.7, 1.0, or 1.3 mg/m^2 bortezomib was given subcutaneously on days 1, 4, 8, and 11 with 40 mg of dexamethasone on days 1–4 every 21 days. Until September 2013, 1.3 mg/m^2 bortezomib had been used as the standard dose, as originally reported [6]. Thereafter, 1.0 mg/m^2 bortezomib was determined as the new standard dose at our center to reduce the risk of side effects on the peripheral nervous system, because large number of consecutive patients [3 of 7 patients (42.9%), including those that were excluded from this study] treated with 1.3 mg/m^2 bortezomib at our center developed peripheral sensory neuropathy (grade <3). Patients >75 years were treated with a dose of 0.7 mg/m^2. Physicians were allowed to reduce the dose of dexamethasone if needed according to the patient's fluid retention level. Patients received prophylaxis with valacyclovir, trimethoprim–sulfamethoxazole, and proton pump inhibitor. The dose of prophylaxis was adjusted according to the patients' renal and hepatic functions. Treatment cycles were continued until the patient achieved the best hematological response, or discontinued due to no hematological response or adverse events. If tolerated, one or two cycles of BD were added after achieving complete response to reduce the chance of future relapse. The median number of BD cycles given to patients enrolled in this study was 3.3 cycles (range 1–7). The BD regimen was discontinued in two patients due to adverse events (ileus and heart failure, respectively). In the HDM regimen, the patients were treated according to our previously reported regimen [7]. Briefly, autologous peripheral blood stem cells were collected using etoposide and granulocyte colony-stimulating factor prior to melphalan administration. A total of 140 mg/m^2 melphalan was then given followed by stem-cell support with or without vincristine, doxorubicin, and dexamethasone (VAD) induction therapy. Only one patient that did not have any organ involvement but was found incidentally to have AL amyloidosis was treated with 200 mg/m^2 melphalan.

Outcome evaluation

Treatment-related mortality (TRM) was defined as death within 100 days after initiation of treatment. Hematological response was classified into four levels according to the international consensus guidelines, i.e., complete response (CR, normal free light-chain [FLC] ratio with negative serum and urine immunofixation), very good partial response (VGPR, difference between involved and uninvolved FLCs [dFLC] <40 mg/L), partial response (PR, dFLC decrease >50%), and no response (NR) [11]. Recurrence rate at month 12 was evaluated among the patients that achieved CR and survived for 12 months or longer. Survival was evaluated by the Kaplan–Meier method.

Statistical analysis

The Chi-square test or Fisher's exact test as appropriate, or *t* test or Mann–Whitney *U* test as appropriate was applied to compare patient backgrounds and treatment outcomes. Log-rank test was used to evaluate survival curves. These analyses were performed using Excel Statistics 2012 for Windows (Social Survey Research Information Co., Ltd, Tokyo, Japan). In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Ethics

This study was approved by the institutional medical ethics board of Shinshu University School of Medicine.

Results

Patient background

Among the total of 234 consecutive systemic AL amyloidosis patients at out center, 20 were treated with BD and 30 with HDM. Table 2 shows the clinical backgrounds of each group. There were no significant differences in parameters between the two groups, including dFLC, NT-proBNP, troponin T (TnT), plasma cell burden, visceral organ involvement, Mayo stage 2012, New York Heart Association (NYHA) class, and Eastern Cooperative Oncology Group (ECOG) performance status, except for age, previous history of other chemotherapy, and transplant eligibility. In the BD group, the median age was higher (63.2 vs. 55.8, $P = 0.001$), the number of patients fulfilling our transplant eligibility criteria was lower (60.0 vs. 96.7%, $P = 0.002$), and the number of patients that had already undergone other chemotherapy was higher (35.0 vs. 0.0%, $P < 0.001$) than in the HDM group. The reasons why the eight patients did not fulfill our HDM eligibility criteria in the BD group were greater age (3 patients), advanced hepatic involvement (3 patients), low cardiac output (1 patient), and both greater age and low cardiac output (1 patient). Among the seven with a history of prior treatment in the BD group, the average number of regimens previously given to the patients before BD was two (range 1–4).

Safety

As shown in Table 3, there was no significant difference between the two groups in TRM (5.0% in the BD group vs. 10.0% in the HDM group, $P = 0.641$). Four patients (20.0%) developed bortezomib-related peripheral sensory neuropathy (all were grade <3; three patients developed grade 1 and one patient developed grade 2 neuropathy). Other adverse events in each group are described in detail in Table 4.

Hematological response

The hematological response rates of each group are shown in Table 3. Although there was no statistically significant difference between the two groups, BD therapy showed trends for achieving higher hematological response rates compared with HDM therapy, i.e., PR or better (90.0 vs. 73.3%, $P = 0.279$), VGPR or better (75.0 vs. 66.7%, $P = 0.529$), and CR (60 vs. 50%, $P = 0.487$).

Recurrence

The recurrence rates at month 12 are shown in Table 3. The numbers of evaluable patients that achieved CR and survived for at least 12 months were 9 and 14 in the BD and HDM groups, respectively. There was no significant difference in recurrence rate between the two groups (22.2% in BD vs. 7.1% in HDM, $P = 0.538$).

Survival

Four patients in the BD group and eight in the HDM group died during the follow-up period, without restriction by cause of death. The overall survival is shown in Fig. 1a. The causes of death in the HDM group were disease progression with or without treatment-related toxicity. In contrast, the causes of death in two of the four patients in the BD group that died were incidental and unrelated to disease progression or treatment; one died due to melanoma and the other died due to intestinal diverticular perforation. Therefore, the adjusted survival curve excluding these two patients was also evaluated (Fig. 1b). In each evaluation, both BD and HDM groups showed good median survival and neither of them reached. The estimated median survival in the HDM groups was more than 15 years. There were no

Table 2 Clinical backgrounds of patients

Variable	BD group ($n = 20$) n (%) or median (range)	HDM group ($n = 30$) n (%) or median (range)	P
Age (years)	63.2 (48–77)	55.8 (44–67)	**0.001**
Sex (M/F)	13/7	17/13	0.556
Subtype (κ/λ)	2/18	10/20	0.092
dFLC (mg/L)	335.37 (0.3–2478.2)	213.27 (2.8–1347.9) ($n = 29$)	0.597
TnT (ng/mL)	0.035 (0.004–0.154)	0.030 (0–0.150) ($n = 14$)	0.151
NT-proBNP (pg/mL)	708.0 (11.3–3310)	579.7 (11.3–2720) ($n = 14$)	0.401
BNP (pg/mL)	92.8 (0–296.0)	92.5 (0–321.9) ($n = 25$)	0.945
Plasma cell count (%)	5.9 (0.6–36.0)	3.2 (0.2–11.2)	0.289
IVS (cm)	1.23 (0.68–2.13)	1.20 (0.54–1.70)	0.921
EF (%)	70.8 (47.4–90.3)	71.1 (52.8–90.0) ($n = 22$)	1.000
Proteinuria (g/24 h)	2.527 (0–6.901)	2.800 (0–12.750)	0.758
eGFR (mL/min/1.73 m^2)	71.9 (40–98)	75.6 (39–126)	0.670
T–bil (mg/dL)	0.64 (0.32–1.37)	0.54 (0.22–0.95)	0.367
ALP (IU/L)	457 (126–2184)	321 (104–1208)	0.992
Involved organ			
Heart	8 (40.0)	14 (46.7)	0.642
Kidney	16 (80.0)	19 (63.3)	0.208
Liver	3 (15.0)	2 (6.7)	0.377
Gastrointestinal tract	6 (30.0)	7 (23.3)	0.599
Peripheral nervous system	2 (10.0)	5 (16.7)	0.687
Autonomic nervous system	1 (5.0)	2 (6.7)	1.000
Soft tissues	10 (50.0)	9 (30.0)	0.154
Mayo stage 2012			
I	11 (55.0)	7 (50.0) ($n = 14$)	0.774
II	4 (20.0)	5 (35.7) ($n = 14$)	0.435
III	2 (10.0)	0 (0.0) ($n = 14$)	0.501
IV	3 (15.0)	2 (14.3) ($n = 14$)	1.000
NYHA class (2≤)	3 (15.0)	1 (3.7) ($n = 27$)	0.298
ECOG PS (2≤)	2 (10.0)	2 (7.4) ($n = 27$)	1.000
Patient who fulfilled our HDM eligibility criteria	12 (60.0)	29 (96.7)	**0.002**
Patient who had past history of other chemotherapy	7 (35.0)	0 (0.0)	**<0.001**

Bold values indicate statistical significance

BD bortezomib–dexamethasone, *HDM* high-dose melphalan with stem-cell transplantation, *dFLC* difference between involved and uninvolved free light chains, *TnT* troponin T, *NT-proBNP* N-terminal of the prohormone brain natriuretic peptide, *BNP* brain natriuretic peptide, *IVS* intraventricular septum, *EF* ejection fraction, *eGFR* estimated glomerular filtration rate, *T-bil* total bilirubin, *ALP* alkaline phosphatase, *NYHA* New York Heart Association, *ECOG* Eastern Cooperative Oncology Group

statistically significant differences in survival rate between the two groups in either evaluation.

Discussion

Both BD and HDM have emerged as epoch-making treatment options, because they showed considerable treatment efficacy for AL amyloidosis [4–6]. The most efficient way to compare the safety and efficacy of BD and HDM is a prospective randomized designed study with adjustment for patient backgrounds. However, this type of clinical trial design is sometimes difficult to apply to diseases in which the number of patients is small and the nature of the disease is fatally progressive, such as systemic AL amyloidosis. Indeed, there have been only a very limited number of prospective studies comparing treatment outcomes [12, 13]. In terms of BD vs. HDM regimens, there have been no prospective or

Table 3 Treatment and outcome of each group

Variable	BD group ($n = 20$) n (%)	HDM group ($n = 30$) n (%)	P
Treatment			
Initiating dose of bortezomib			
0.7 (mg/m^2)	1 (5.0)		
1.0 (mg/m^2)	14 (70.0)		
1.3 (mg/m^2)	5 (25.0)		
Patient who received induction chemotherapy before HDM		23 (76.7)	
Dose of melphalan			
140 (mg/m^2)		29 (96.7)	
200 (mg/m^2)		1 (3.3)	
Outcome			
Treatment-related mortality	1 (5.0)	3 (10.0)	0.641
Hematological response			
≥PR	18 (90.0)	22 (73.3)	0.279
≥VGPR	15 (75.0)	20 (66.7)	0.529
CR	12 (60.0)	15 (50.0)	0.487
Recurrence rate at month 12	2 (22.2) ($n = 9$)	1 (7.1) ($n = 14$)	0.538

BD bortezomib–dexamethasone, *HDM* high-dose melphalan with stem-cell transplantation, *PR* partial response, *VGPR* very good partial response, *CR* complete response

even retrospective studies to date. Therefore, this is the first report comparing these two important treatment regimens.

With regard to patient backgrounds, there were no significant differences between the two groups in most variables, but median age and the number of patients ineligible for transplant were significantly higher in the BD group (Table 2). This finding is quite reasonable considering the eligibility criteria for each regimen at our center (Table 1). As HDM therapy is invasive and demanding, it is recommended to select suitable candidates in better overall condition to achieve good outcome safely [14]. In contrast, our BD eligibility criteria are simpler and less strict (Table 1), and therefore, it can be applied in much older patients compared with HDM. This is because the BD group included many older patients (approximately 10 years older on average compared to HDM), which resulted in fewer patients fulfilling the transplant eligibility criteria. The number of patients with a previous history of other chemotherapy was also significantly different between the two groups, i.e., 35% in the BD group and 0% in the HD group ($P < 0.001$). This may have been because the BD regimen is usually used as "second-line" therapy in patients' refractory to other forms of chemotherapy, and not as the "first-line" therapy, in contrast to HDM [5].

Tables 3 and 4 along with Fig. 1 show treatment outcomes (safety and efficacy) in both groups. In this study, TRM was used to evaluate major treatment safety and there was no significant difference between the two groups (Table 3). In the original report of BD, the rate of death within 100 days was reported to be 2 of 18 patients (11.1%) [6]. Among HDM regimens, the TRM rate was reported to be 12–13% in the early 2000s [15, 16], which decreased to 7% by refining the eligibility criteria around 2010 [17]. Tsukada et al. reported that TRM was 10% in a single-institution study setting in Japan [18]. Considering these results, the safety of both BD and HDM regimens at our center seems quite reasonable and as good as those reported previously. In addition to TRM, treatment-related adverse events were also analyzed to evaluate the safety of both regimens. As shown in Table 4, hematological toxicity, fatigue, digestive symptoms (nausea/anorexia), infection of undetermined origin, and cytomegalovirus antigenemia were significantly severe in HDM regimen, which were understandable considering the high dose of melphalan used in this regimen. There were no significant differences in incidence rates of other adverse events, including peripheral sensory neuropathy and herpes zoster, between the two groups. However, patients treated with HDM tended to show more severe adverse events, because duodenal perforation, catheter-related infection, disseminated intravascular coagulation, deep venous thrombosis, ventricular tachycardia (Torsade de Pointes), acute kidney injury, and multi-organ failure were only seen in the HDM group, whereas ileus and peripheral sensory neuropathy were only seen in the BD group. With regard to the bortezomib-related toxicity to the heart, there have been previous reports describing possible cardiotoxicity of bortezomib [19–22] and one meta-analysis review that could not

Table 4 Adverse events of each group

Event	BD group ($n = 20$) n (%)	HDM group ($n = 30$) n (%)	P
Adverse events (grade 2≤)			
Neutrophil count decreased	1 (5.0)	26 (100.0) ($n = 26$)	**<0.001**
Febrile neutropenia	0 (0.0)	22 (88.0) ($n = 25$)	**<0.001**
Anemia	1 (5.0)	26 (100.0) ($n = 26$)	**<0.001**
Platelet count decreased	7 (35.0)	26 (100.0) ($n = 26$)	**<0.001**
Fatigue	3 (15.0)	25 (100.0) ($n = 25$)	**<0.001**
Nausea/Anorexia	8 (40.0)	25 (100.0) ($n = 25$)	**<0.001**
Ileus	1 (5.0)	0 (0.0) ($n = 25$)	0.444
Duodenal perforation	0 (0.0)	1 (4.0) ($n = 25$)	1.000
Respiratory tract infection	1 (5.0)	1 (3.8) ($n = 26$)	1.000
Urinary tract infection	0 (0.0)	0 (0.0) ($n = 26$)	1.000
Catheter-related infection	0 (0.0)	2 (7.7) ($n = 26$)	0.498
Sepsis	1 (5.0)	3 (11.5) ($n = 26$)	0.622
Disseminated intravascular coagulation	0 (0.0)	1 (4.0) ($n = 25$)	1.000
Deep venous thrombosis	0 (0.0)	1 (4.0) ($n = 25$)	1.000
Heart failure	1 (5.0)	3 (12.0) ($n = 25$)	0.617
Ventricular tachycardia (Torsade de Pointes)	0 (0.0)	1 (4.0) ($n = 25$)	1.000
Acute kidney injury	0 (0.0)	4 (16.0) ($n = 25$)	0.117
Multi-organ failure	0 (0.0)	3 (12.0) ($n = 25$)	0.242
Peripheral motor neuropathy	0 (0.0)	0 (0.0) ($n = 25$)	1.000
Peripheral sensory neuropathy	1 (5.0)	0 (0.0) ($n = 25$)	0.444
Others (without grading scale)			
Infection of undetermined origin empirically treated with intravenous antibiotics	9 (45.0)	23 (100.0) ($n = 23$)	**<0.001**
Cytomegalovirus antigenemia treated with intravenous ganciclovir	1 (5.0)	9 (34.6) ($n = 26$)	**0.028**
Herpes zoster	0 (0.0)	0 (0.0) ($n = 25$)	1.000

Bold values indicate statistical significance

detect significant risk of cardiac events [23]. In the present study, one patient in the BD group (5.0%) and three in the HDM group (12.0%) developed heart failure, and none in the BD group (0.0%) and one in the HDM group (4.0%) developed ventricular arrhythmia; these differences were not statistically significant. Furthermore, the bortezomib-based regimen is now considered to be effective to improve survival in patients with advanced cardiac involvement [24]. Therefore, it is both important to consider the risk of toxicity and to take advantage of efficacy on the heart when treating patients with bortezomib. Careful monitoring of cardiac function before, during, and after treatment is recommended.

With regard to the hematological response, BD treatment tended to provide a higher response rate compared to HDM in this study, but this finding was not statistically significant probably due to the small number of patients (Table 3). Our patients in the BD group achieved CR at a rate of 60%, which was superior to that in the original report (44%) [6]. However, we cannot simply compare these results, because patient backgrounds were different between studies. The CR rate in the HDM group at our center (50%) was slightly better than that reported previously in a large cohort study performed at the Mayo Clinic (40% in 454 patients) [25] and was as good as that described in a previous report from Japan (52%) [18]. Notably, our center achieved this result with a reduced dose of melphalan (total 140 mg/m^2) compared to the standard HDM dose (total 200 mg/m^2), even though the reduction of melphalan dose usually results in a lower hematological response rate [15]. This result may have been due to the use of VAD induction therapy at our center. The treatment strategy designated as the "risk-adapted approach," which involves adjusting the dose of melphalan based on the patient's condition, was already reported [26], and our standard dose (140 mg/m^2) is considered to be a reduced dose for the patients with intermediate risk. Therefore, reduced melphalan dose with some induction therapy may be an option to perform HDM regimen safely with hematological response rate as good as that with the original dose. In this study, there was no significant difference between the

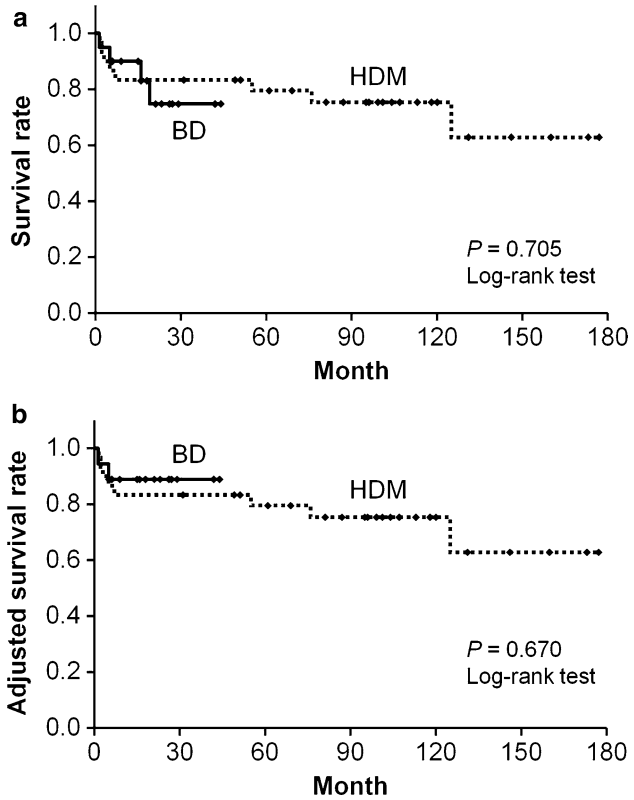

Fig. 1 Overall survival and adjusted survival curves of the two groups. **a** Overall survival curves of bortezomib–dexamethasone (BD) and high-dose melphalan with stem-cell transplantation (HDM) groups. **b** Adjusted survival curve excluding patients that dead due to causes unrelated to disease progression or treatment. No statistically significant differences were detected in either analysis

two groups with regard to recurrence rate over a short period (12 months) (Table 3). We could not perform long-term analysis because of the relatively short follow-up period of BD patients in the present study (Fig. 1). Further studies evaluating the recurrence rate are required to compare the long-term effects of the two treatments.

As mentioned in "Results'', the adjusted survival (Fig. 1b) was evaluated in this study in addition to the overall survival (OS) (Fig. 1a), because deaths unrelated to disease progression were only observed in the BD group. This may have been due at least in part to differences in patient backgrounds. The greater number of aged patients in the BD group may have affected the higher rate of progression-unrelated deaths, because older patients have higher rates of incidental complications. In fact, two patients that died due to causes unrelated to disease progression were 59 and 75 years when they started BD treatment; both were older than the median age of the HDM group (Table 2). In contrast to OS, the adjusted survival curve showed a slight trend of better outcome in the BD group. However, there were no significant differences between the two groups in both survival evaluations, as the small number of patients and relatively short follow-up period of the BD group may have affected the statistical power (Fig. 1). Our performance regarding OS in the HDM group (estimated median OS > 180 months) was also favorable compared to a previous large cohort study (113 months) [25]. No adjuvant therapy was given to those patients after HDM at our center, but if they relapsed or their organ involvement progressed, they were re-treated accordingly on a case-by-case basis.

In conclusion, no statistically significant differences were detected in this study regarding TRM, hematological response, and overall and adjusted survival rates between the two groups. However, it is noteworthy that BD achieved this result in patients with significantly poorer clinical backgrounds (i.e., greater age, poor transplant eligibility, and refractoriness to other chemotherapy) compared with HDM. A prospective randomized trial with equal patient background settings would likely yield different results, and further well-designed studies are required.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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